COLLIER, JAMES.

T. R. Elliott

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Inventions and the Outlook in Neurology

being

THE HARVEIAN ORATION

delivered before the Royal College of Physicians of London on 18th October 1934

by

JAMES COLLIER, M.D., F.R.C.P.

Consulting Physician and Emeritus Lecturer in Neurology, St. George's Hospital

Physician to the National Hospital for Nervous Diseases

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INTRODUCTION

We are met for the two hundred and seventy-eighth time to do honour at his command to the outstandingly illustrious Fellow of this College, whose success was so great in his own time that he would hand down the methods by which he thought it had been achieved to all his successors that none might be ignorant thereof.

And whose love for this College was so great that it was the dominant wish of his heart that his name should be honourably mentioned within these walls, once in every year, that the love and harmony with his associates of this College, which he had enjoyed and valued so much, should be regularly placed before you, with his wish and exhortation to you that it shall continue unbrokenly, and that those who followed him as benefactors of this College, either by gifts, by brilliant achievement, or by high usefulness, should be mentioned by name for their honour and for our emulation.

He placed a Trust and Benefaction with this College to secure that we should meet each year to fulfil his wishes and thereafter join in a loving feast.

The illustrious names of those into whose hands it has been given to deliver to you the messages of Harvey, which is a role of the most renowned in English Medicine, the high quality and ever varied manner in which they have expressed them during long ages, the success of their personal efforts as followers of Harvey, and the atmosphere of progress and of love, peace, and harmony which is so redolent within this College, bears full witness to the loving care and the success with which Harvey's sacred trust is nurtured. I am deeply grateful to you, President, for the honour that you should deem me worthy and capable of carrying on the great tradition of the Harveian Orator.

It is my easy office to make honourable mention of

William Harvey in drawing your attention to the gifts of wisdom and personality which made an unqualified success of his life and which must have brought him high satisfaction lasting to the end of his long life. Comfortable in circumstances, I imagine his journeyings in search of education from Cambridge to Paris and thence to Padua as free from difficulties and privations and rather of the order of 'Costly thine habit as thy purse can buy', and his graduation at Padua as completed in comfortable conditions. For the charming Anatomy School of Fabritius, still in its original state as when Harvey occupied his place there, was largely free from the interference of Church and State. There no priest watched the anatomy lessons, hampering and interfering lest anything be lost in view of the resurrection, as happened in the not far distant school of Bologna, but the remains were frankly incinerated in modern fashion.

Throughout his life Harvey was carried by the pleasure and contentment of searching out the secrets of Nature by way of experiment and observation with success, and he was well aware that he was superior in mind, in method, and in results to his contemporaries in Medicine.

As a destroyer, reformer, and inventor he was gentle. When he is described to us as an irascible little man whose hand was often upon the pommel of his dagger, we must take it that this was for emphasis only, for there is no story that he drew it upon any one or offended thereby. He was not so quick and forceful as to offend and oppose his new discoveries to 'captious criticism and ungenerous mistrust', nor so slow as to lose the prize of their universal acceptance within his lifetime. In England his conquest was by surrender without a battle. Abroad, his doctrines met with considerable opposition which must have added interest for Harvey and which did stimulate him to write his second work on the heart in 1648, twenty-one years after his first

publication. But even in this opposition Harvey had the high satisfaction of seeing one of his strongest opponents, Plempius of Amsterdam, unconditionally bury the hatchet, and become one of his ardent advocates. In the end, too, Paris surrendered, and Harvey's victory was complete.

Harvey, as a revolutionary, escapes unscathed and triumphant, while Servetus, his immediate predecessor in aiding the discovery of the circulation, of whose work, however, Harvey had no knowledge, with Sempelius and others were burned at the stake for their innovations. Harvey was fortunate in that history has given us little of the details of his life which allow reference to shortcomings and failures. Willis said of him that all his public actions were made with propriety and grace, and we are left with the impression of a comfortable, busy, successful, and lovable genius who made the best of the true enjoyment of life. Such an impression seems to me to beam out of the fine portrait by Janssen which is behind the President. His writings convey to me the same feeling. It is true that he writes sharply against the methods of his time, now and then, as in the words 'Experiment leads to success whilst empty assertions, mere suppositions and false sophisticated reasonings end only in error and delay'. But he was largely impressed by his sense of the defects of his contemporaries in Medicine, and he was well aware of his own superiority and of the high importance of his own discoveries. In his own words, the worst suffering he had ever to endure was the loss of his writings and records of his work which were destroyed when his house was pillaged by the mob because of his constant loyalty to his Royal Master and patient, Charles I, during the revolution, and this he seems to have met with philosophic forgiveness.

After a long life of intense industry, for his dissections, pathological inquiries, and contemplations were unceasing—a life of such continual success and satisfaction, it is a little difficult to follow the historian

Cumston that Harvey retired to Lambeth a disillusioned man, for what could have disillusioned so comforting a life; rather let us think that his last days were full of the comfort of success.

For us, his posterity, Harvey is the first to pick up the threads of experiment and observation begun by Galen in the correct deductions from his lesions of the spinal cord in frogs and rabbits, continued by Aristotle, and thereafter broken for 1,500 years; and he is styled the 'father of modern Physiology'. From the manner of his work in experiment and in observation of proofs, he is the inventor of modern methods of research. From the law which he laid down of 'Omne vivum ex ovo' he is the starting-point in the idea of evolution. From his inspired flight of thought expressed in the words 'Epidemic, contagious and pestilential diseases scatter their seeds and are propagated to a distance through the air and in hidden fashion silently multiply themselves by a kind of generation' he is the prophet of Bacteriology to come. He is the inventor of the circulation of the blood. To his colleagues and to his patients he was the 'Beloved Physician', and in this College he receives homage upon each St. Luke's Day as its most illustrious Fellow. Harvey's exhortation to us is 'to search out and discover the secrets of nature by experiment and observation'. The first experiment is in a flight of thought, a wandering of the mind which begets a sudden new idea, a flinging away for the moment of all we have taken on trust as Gospel, or sometimes an attempt to explain in words to others what we ourselves do not understand has brought discovery. No one ever made successful experiment but he had already conceived that something would happen from it, nor an invention without the idea as to how it would work. However much Harvey may have denounced mere speculation in others, yet guided by his careful observation it was his primary method of work. He had surely a firm conviction that the blood did circulate and in a certain way before he

put his experiment into being. He had surely conceived that the 'to and fro', 'ebb and flow' movements of the blood which had been Gospel since the time of Galen could not be and was driven by dissatisfaction to make his great discovery. There is no method in discovery, sometimes there seems to be a high element of fortunate chance. Great knowledge is not always essential; sometimes it seems a hindrance to personal progress, for much of a very wide knowledge is of necessity taken on trust without even reasonable personal analysis. A castle builded in the air by a highly knowledgeable fancy, in the course of a week-end of leisure, and a lifelong plodding with microscope and stains have both on occasion brought an equal advance in Medicine though the labour entailed in the two events is so unjustly different. It is remarkable that in former times when knowledge of Medicine was scant, the pioneers in expressing their brief views upon physiology and disease, and particularly in teaching their pupils, gave explanations that would sum up in a nutshell our accepted knowledge of the present day after a century of discovery and proof. Such flights of thought, such lucky hits upon the real truth are, I submit, dismissed by posterity as dreams without discovery and without appreciation of their greatness. They are in reality potential discoveries not followed up; probably from lack of continuing interest, certainly from the lack of methods and of knowledge as to how to find proofs. I shall presently, in attempting to hold your interest upon inventions and their effect in the progress and present outlook in Neurology, draw your attention to several prophetic flights of thought, all of which were great, and some of which resulted in great advance of knowledge.

The Benefactors of this College, by high personal achievements of fame by their loving work for the College to the advancement of its prestige and power throughout the Empire and the World and by their gifts, enabled us from early times to carry on our lectures

for the education of the profession, and for the stimulation and reward of those chosen to give them because they had followed the call of Harvey to successful experiment and observation, and now enable us increasingly to fulfil the important office of helping those who are engaged in promising paths of experiment and discovery, and in providing a living wage for the training of the young in methods of experiment and research, confer an invaluable asset to this College and to the advancement of science, and I exhort you all to lend your aid.

INVENTIONS AND THE OUTLOOK IN NEUROLOGY

My address to you is upon 'Inventions and the Outlook in Neurology'. I have chosen the word 'invention' as best fitting the bringing in of a new idea—an invention of the mind which has not occurred before, which may prove to be a discovery of the truth or may fail as a false hypothesis, as well as the bringing in of a demonstrable fact or new method. It is a story of remarkable flights of fancy long ago which are now the proved facts of our belief, and of other 'castles in the air' which became for the time the strongholds of the scientific world, who dwelt therein for a long time, contented because the building was beautiful to think upon and could be altered at will by successive occupants according to their fancy and who would not see a notice long before put up, that no mortar or foundations of 'busy common sense' are available in this country. These castles are now largely deserted, and such as dwell therein are not in security.

Wonderful inventions for the study of the structure of the nervous system and tireless research have resulted in knowledge practically complete of the most intricate and marvellously beautiful network with input paths leading from the outside world and output paths leading to the muscles for action, almost incredible in its extent, everywhere continuous and so complicated that it is impossible to prove or to conceive how it works except in a few of its lower and grossly mechanical regions. This vast and solid edifice of proved knowledge of structure has added little to our knowledge of function and disease. But it is a very important little, for it is all we have, and it is concerned with the lower and more grossly mechanical regions of the spinal cord and brain-stem. This quarry has been worked out and labour in

it has wellnigh ceased. Delving into the function of the nervous system by experiment has reached so high a refinement that the signals by which each part works can be made visible and audible. Always the same signals in every part alike, only more and more rapidly repeated as the message becomes stronger and more urgent, and the end result of these fine labours is some knowledge as to how the lower and simpler regions, namely the spinal cord and brain-stem, work. To the greatest of living physiologists, who has spent a long life in the experimental study of the nervous system—the Rede Lecturer for last year—Sir Charles Sherrington, the highest and largest part of the nervous system, the brain, is still mainly a form and a series of events, and his ignorance of much of their relation bids him despair. Yet proclaiming himself an optimist as opposed to a defeatist, he puts the question, 'Will it ever be possible to understand the nervous system?'

In the recognition and distinction of the nervous diseases the past century has brought an ever-increasing and now almost complete knowledge which has not yet and will not reach finality, for disease is subject to evolution and devolution and disappearance at least for a time. The causation of many of the diseases is now clear, and of recent years studies of biochemistry and of virus infection have brought suggestions of what the future may discover in maladies of which we do not know the cause. Methods of treatment, though far behind those of diagnosis, are advancing, and at the moment we seem to be in possession of means of diagnosis and treatment which will surely remove the terrible diseases General Paralysis and Locomotor Ataxy from the community. Yet the fact remains that the four most prevalent and relentless of the nervous diseases, Disseminate Sclerosis, Progressive Muscular Atrophy, Paralysis Agitans, and most of the Vascular Diseases come before us without any clue whatsoever as to their cause and without any means whatsoever of their prevention, nor in the case of

Progressive Muscular Atrophy even of the slightest amelioration.

These are the hopes of the immediate future.

Franz Josef Gall. The Pyramidal Tract. The Function of the Brain. Cerebral Localization.

The means by which invention begins, the arousing of that lasting interest which does not rest until discovery is made, is often intangible and a thing perchance and of personality, but sometimes it has been recorded, and I may introduce the great discoveries in neurology with an instance. At the end of the eighteenth century a self-conscious lad pondered upon his disability to promptly answer in class the things he knew well, and concluded that it was because Nature had not given him a fine forehead and prominent eyes. His interest in the brain and speech never thereafter left him. He became a very great anatomist of the nervous system, and he proved by his dissection the definite structural path from brain to muscle partly crossing in the medulla—the pyramidal path—and his proof was then and there accepted by the knowledgeable world for all time. Like Harvey he was not the first inventor of this idea, but like Harvey he gave such proof of its truth that no one wished to deny it. Gall's discovery of a definite pathway conveying movement from brain to muscle was the foundation of all subsequent paths of function within the nervous system. Gall in his early days laid down the truest conception of the brain as the exclusive seat of the highest nervous functions only. By his conception of speech as a function of the forward part of the brain he was the inventor of the idea of localization of function in the brain. It does not detract from the greatness of the discoveries of this remarkable man that he went over into Phrenology and died discredited, torn from his high position by the prophetic denunciation of Flourens that there are no separate highest functions to be localized in the brain but that all are interwoven. Around his

conception of cerebral localization such a war was raged during the nineteenth century—complete defeat at first, and then after years complete triumph, and then later defeat not yet complete—as has stimulated more investigation and produced more useful discovery than any other event in the history of neurology. At the moment the localization of function in the brain is presumed by our physiologists, but admittedly without means of scientific proof. The only proved localization of function is that of the conduction tracts—the input and output paths which connect the animal with the outside world.

Purkinje. The Discovery of the Nerve-cell. The Invention of Histological Technique.

In 1835 an Austrian priest of gipsy family became possessed of a microscope, and like the inventor of bacteriology, Leeuenhoeck the linen-draper, he became interested therein. In a short space of time he had discovered the nerve-cell, which added to Gall's nerve-tract was the instigation of all later discovery. He gave to the world in a short space of time a hardening reagent, bichromate of potash, which would allow sections of soft tissue to be cut, a machine, the microtome, to cut the sections, a stain, carmine, to bring out the details, a clarifying reagent, oil of cloves, which made microscopic examination possible, and Canada balsam with which permanent preparations could be made. Purkinje's inventions were epoch-making in the progress they caused. He was removed from the priesthood and made Professor of Physiology at Breslau. As the fruits of these fine inventions came at once the establishment of the cellular theory of tissues from Schleiden and Schwann and the cellular pathology of Virchow. Rosenthal demonstrated that the nerve-tract was made up of fibres springing from the nerve-cell, and Schwann found the insulating sheath which protects the nerve-fibres. Waller by his methods of degeneration commenced the tracing of the nerve-tracts within the nervous system. Thereafter with the

wonderful discoveries and patient work largely of the German School, in which the names of Weigert, Edinger, Cajal, and Golgi stand out, the structure of the nervous system has been made known with such delicacy of detail, such intricacy of connexions, such enormity in amount as to be altogether outside the possibilities of present-day comprehension of the relation of structure to function except in its lowest and least complicated regions. It is referred to nowadays as one entity—'the nervous network'—just as it was first named the 'sensorium commune' a century and a half ago.

Georg Prochaska. The Invention of Reflex Action.

In 1784 a Professor of Anatomy in Moravia wrote a very short account of the nervous system, and in attempting to explain how it worked, his flight of thought rose to almost the exact present-day conception. He said that 'physical and mental stimuli acting upon ascending nerves are conveyed directly through the ganglia and network of nerve threads, to be reflected thence by means of descending nerves with a result in action'. This wonderful discovery in thought of reflex action, arrived at so far as we know without definite experiment, is the foundation of most of what we now know as to the way in which the nervous system works. I will ask you to compare these words of Prochaska with those of Sir Charles Sherrington in the Rede Lecture for last year: 'Brain and Nerve are but a skilfully laid train of powder between the muscles it fires and the restless world outside which fires it. The question who pulls the trigger is easily answered. It is the outside world.' And again, 'an animal's motor behaviour where the brain nets are large excels in variety and nicety but it fails to offer anything radically different from reflex action elsewhere.' By actual experiment Sir Charles Bell at Middlesex Hospital, Majendie in Paris, and others discovered the function of the spinal roots as input and output paths by which reflex action is carried on, and Bell most

importantly first conceived of the long reflex processes which went as high as the brain. Later Marshall Hall with many experiments brought in the details of the reflex spinal arc, but he denied the long reflexes and wished to make the essential local function of the spinal cord reflex action, in contrast to that of the medulla, which was for him automatic and the brain volitional. Now all unconscious action is reflex action. The great Pavlow and others have shown us how large a part reflex action plays in conscious action and behaviour. It is when we arrive at those processes in the brain which are not traceable to outside stimuli and cannot be reduced to the principle of reflex action that our knowledge as to how the mechanism works fails rapidly and finally. I may perhaps give you a simple example of the utter dependence of high cerebral function upon a reflex process. When I speak to you my speech does not flow out from well-trained speech centres in the brain as does water from a full cistern. I must have an immediate and delicate reflex return reaching me by my ears and by the sensation of movement of my lips which keeps me instantly informed as I go along that what I am saying is in correct pattern. If anything blocks the path of both those reflex actions I shall not be able to finish even a sentence, my speech though long practised will break down at once into an inarticulate jargon in which both words and pattern disappear. If through a faulty attention to my reflex signals I miss out an important word, my meaning tends to become unintelligible to my listeners and my speech an imperfect function.

Hughlings Jackson. The Hypothesis of Nervous Function.

Hughlings Jackson, who is the pride of English Neurology as Harvey is of English Medicine, was an inventor who greatly influenced and moulded the present position of neurology. In method he was the ablest deducer from what seemed to be the minimum of observation, but his chief genius was that he was a relent-

less dreamer who criticized with a positive inquisition the flights of thought to which he rose, and apparently only gave to the world those which survived this ordeal, for there is hardly a thing of his which has not borne the test of time. He conceived that Nature had builded the nervous system upon the same pattern of function in its several parts. And that at the lower stations, the local requirements of the individual segments of the body were looked after, but that at higher levels the requirements of everything below were subserved in increasingly compound proportion, and that at the highest levels the nervous system was concerned with the requirements of the animal as a whole—perhaps some of these concern some parts of the brain more than others. This remarkable conception, which arose when popular belief was convinced that centres for separate functions in the several parts of the brain were ascertained facts, is substantially the proved knowledge of the present day. The supporters of local centres of function in the brain had forgotten their parent Gall and the simple but emphatic statement by which he was overthrown, 'there are no such separate functions for localization'. I may perhaps put it like this: the functions of seeing, hearing, and feeling are clearly separate so far as the nerve-terminations in the eye, ear, and skin are concerned, but when a stimulus from one of these organs reaches the nervous network, it becomes modified by all the other stimuli which are incoming at the moment, and the higher in the nervous system it spreads this modification increases, so that it becomes more and more difficult to think or to speak of it as a stimulus in one isolated function such as vision, hearing, or feeling. Hughlings Jackson wrote: 'I cannot conceive any function of vision apart from the function of movement.' I will give you a common example of the difficulty in which the principle of local function in the brain, other than that in the tract of output and input, has always placed the clinician. A patient of mine had a large tumour in the

right occipital lobe which was removed with complete success, but the lobe which was supposed to be the seat of one half of his visual life was destroyed. For the next twenty years, though he could not see to his left side he carried on his occupation as a highly skilled metal-worker, nor was his judgement in filing true to one-hundredth of an inch in the least impaired, nor his visual memory or appreciation in any way lessened. It seems clear that the local loss of function which one sees daily from local lesions of the brain is always the result of the blocking of the input and output paths, and I have arrived at the conclusion that when mental defect occurs from a not too extensive local lesion of the brain it results from a block upon those important tracts which put the several regions of the brain in touch with one another, and never from lesions of the higher regions of the brain which were formerly supposed to subserve mental functions exclusively.

Therefore we have now the vast expansion of the brain in the words of Sherrington, 'as an input and output signalling system which is newly arisen as a gigantic combining mechanism for the signals from the outside world and as a dominant part of the nervous system which tends to deal with the requirement of the animal as a whole more than does any other part.'

Robert Bentley Todd. The Invention of Locomotor Ataxy and of Peripheral Neuritis.

One of the most remarkable inventions in a flight of thought, to become a proved principle a century later, came from the distinguished founder of King's College Hospital, Robert Bentley Todd, in an attempt to explain lead paralysis to his pupils. He said: 'I believe that the muscles and nerves are early affected and that at a later period the nerve centres may become implicated. The nervous system is thus first affected at its periphery in the muscles and nerves and the poisonous influence continuing the contamination gradually advances towards

the centre.' Recently it has been shown by Aub and others that in lead paralysis accumulation of the lead occurs first in the affected muscles and that the poison seeps up through the nerve-endings into the nerves and reaches the central nervous system. The principle that the nerves are protected by their fatty sheaths against the advent of poisons and infections everywhere but where the nerve-endings are exposed in the extreme periphery, and that it is only in these exposed terminals that noxious agents can gain access and that they travel by a process of seepage along the nerve-filament to gain the central nervous system, is now generally accepted. Viruses that affect the nervous tissues travel in the same way, and seemingly spread universally. As the only nerve-terminals exposed to the outside world are the olfactory terminals in the nose, it follows that virus infections of the nervous system must be acquired by droplet infection of the nose or by wounds which expose the nerve-filaments to infection. Dr. Todd, who was by far the greatest clinical neurologist Britain had produced until the time of Hughlings Jackson, was the first to begin the breaking up of the spinal diseases, at that time all classed as 'paraplegia', by his remarkable invention of locomotor ataxy as a distinct clinical entity. He did this with his usual vivid imagination and his customary absolute faith in his own powers of clinical and post-mortem observation. He described his invention in 1847 in these words:

'I have observed that lesion of the anterolateral columns impairs the sensitive power to an extent proportional to the amount of the lesion and that perfect sensibility is compatible with total local destruction of the posterior columns—the posterior roots remaining intact. Neither anatomy, pathological observation nor experiment justify me in concluding that the posterior columns are the ordinary channels for the transmission of sensitive impressions made upon the trunk and extremities. I have long been strongly impressed that the office of the posterior columns is very different from any yet assigned to them. They may be in part

subservient to the functions of the cerebellum in regulating and co-ordinating the movements necessary for perfect locomotion. The attribute of locomotive power rests upon the connexion of the posterior columns with the cerebellum and the probable influence of that organ over the function of locomotion and the maintenance of the various attitudes and postures. An analysis of locomotive actions shows that they are dependent upon the influence of physical impressions upon that part of the spinal cord from which the nerves of the lower extremities are derived. The support of the centre of gravity of the body requires that the muscles of the lower extremities, the pillars of the support of the trunk, should be well contracted in a degree proportional to the weight they have to sustain. The contraction of these muscles seems well provided for in an arrangement for the development of nervous power by a stimulus propagated to the centre, and then reflected upon the motor nerves of these muscles. Thus the posterior columns come into action in balancing the trunk and in harmonizing its movements with those of the lower extremities. Two kinds of paralysis may be noticed in the lower extremities, the one consisting simply in the impairment or loss of volitional movement, the other distinguished by a diminution or total loss of the power of co-ordinating movements. In the latter form, while considerable voluntary power remains, the patient finds great difficulty in walking and his gait is so tottering and uncertain that his centre of gravity is easily displaced. In this variety of paralysis I venture to predict disease of the posterior columns, the diagnosis being founded upon the views of their functions which I now advocate, and this I have found to exist on post-mortem inspection. In looking through the accounts of the recorded cases in which the posterior columns were the seat of the lesions, all seem to have commenced with this incoordination of the locomotive powers.'

Todd wrote these words four years before Romberg wrote his work, eight years before Russell Reynolds described the disease as 'muscular anaesthesia', and eleven years before Duchenne christened it 'progressive locomotor ataxy'.

Quincke. The Invention of Lumbar Puncture.

In the year 1891, and in a quiet way, came an invention which slowly led the most astounding progress in

our knowledge of nervous disease and of its diagnosis differentiation and treatment. No event in the history of neurology has brought so many assets as has the invention of lumbar puncture. Quincke of Magdeburg conceived that he might relieve the symptoms of hydrocephalus by draining the cerebrospinal fluid. Six years previously Corning in America had drained the fluid for the treatment of tuberculous meningitis, but Quincke was the first to make his invention known throughout the world. The discovery of changes indicative or characteristic of certain diseases in this hitherto unimportant fluid soon followed, and lumbar puncture has become a routine in diagnosis and treatment. It has given us the means of speedy relief from the agonizing pain and danger of increased intracranial pressure, the cure of epidemic meningitis, of cerebral uraemia, of bromide and barbitone poisoning, and it has given us spinal anaesthesia. It has led to the discovery of the clinical features of meningeal haemorrhage and its common cause in leaking aneurysms, to the easy recognition of the many forms of meningitis, and gives definite indications of prognosis in the sugar, chloride, and cell content. Pressure upon the spinal cord and occlusion of the cerebrospinal space are now easily discovered by the increased protein in the stagnant fluid, and the exact site of the pressure can be made visible by the injection of lipiodol, which is opaque to X-rays. Our whole conception of peripheral neuritis has been changed from one of an affection of the peripheral nerves into one of a malady creeping upwards along those nerves into the roots and central nervous system by the constant discovery of changes in the protein content of the cerebrospinal fluid and often by the presence of large numbers of cells therein. In spirochaetal infection lumbar puncture has discovered that when the nervous system is affected this occurs at quite an early stage, and this infection often dies out. Those subjects in whom signs of infection persist in the cerebrospinal fluid are alone

liable to the advent in after years of General Paralysis and Locomotor Ataxy, and in the early treatment of such patients with malarial infection, mercury, and arsenic we think that we have now a certain means of stamping out altogether these terrible diseases from the community. Quincke's simple invention has caused an almost unmeasurable bound forward in our ability.

Von Wagner Jauregg. Malarial Therapy.

When von Wagner Jauregg of Vienna invented the treatment of General Paralysis by malarial infection he re-used an ever-popular method of treating nervous disease. For Hippocrates mentions it and Aretaeus counsels it for the treatment of epilepsy, and from the sixteenth century even as late as 1850 it was one of the established treatments for epilepsy. Perhaps it was the association of epileptic fits with madness in General Paralysis which led Dr. John Mason Good in his *Text Book of Nervous Diseases* of 1824 to advise that such patients should be at once sent to the marshes of Essex to acquire a sharp attack of the marsh fever. Jauregg lost interest in his invention for many years, but reviving it gained the Nobel prize with his results.

Von Economo. The 'Encaged Virus'.

Von Economo in 1921 conceived of a virus which, gaining access to the nervous system by the exposed olfactory terminals in the nose, becomes an 'encaged virus' within the nervous system with no means of getting out, and which if not conquered by the natural processes might remain indefinitely to cause either recurrences of symptoms from time to time or alternatively to progressive degeneration and death of the nerve-elements. On this hypothesis he would explain the varying results of lethargic encephalitis, now a permanent cure, now a series of recurrences, and often again an advancing and resistless break up of nervous function long after the initial infection and when the primary

symptoms had been slight. He would explain the absence of case-to-case infection in lethargic encephalitis and in poliomyelitis that the virus is encaged by the time the symptoms appear and cannot get out to infect others.

Infection can only occur from carriers and in the presymptomatic period of these diseases when the virus is a surface saprophyte in the nose. Nicolau and Galloway, at the Pasteur Institute, have shown how the viruses infecting the nervous system travel along the nerve-threads to even the remotest parts of the nervous system, and that any peripheral nerve-twig if dissected out and placed in the nervous system of another animal will cause infection. In the course of the universal spreading of the virus, the remarkable brightly staining 'inclusion bodies' in the nerve-cells and the lymphocyte exudations along the nerve-fibrils remain as evidence of its passage. This complete invasion of the nervous system may occur without producing any symptoms at the time.

In the case of one encaged virus—that of herpes zoster—it seems clear that a local lowering of vitality of part of the nervous system by reason of injury, exposure to cold, arsenic administration, and other causes, may break the encagement, and the virus discharges outwards along the debilitated nerve to flower upon the skin in the characteristic shingles, and that flowering upon the skin is the only means of continuing the species and infecting other members of the community. After that flowering the virus within the nervous system dies, as does the annual plant in the garden after its flowering. But it may happen that the debilitated nerve along which the virus is able to discharge is a motor nerve, in which case the virus is unable to flower, but it may cause much commotion with lymphocytic swelling in the nerve, and this is undoubtedly the cause of many of the motor-nerve paralyses for which we have hitherto had no causal pathology, the commonest being Bell's facial paralysis from exposure to cold. Von Economo's principle of an infection encaged within the nervous system, existing

and producing changes, without causing symptoms or alteration of function perhaps for years, and finally destroying, is likely to bring important developments in the future. As a clinical fact it has been known for long years in the end results of spirochaetal infection, unrecognized at its advent and symptomless perhaps for half a lifetime.

I will speculate for a moment upon Disseminate Sclerosis. That this malady never appears before the age of puberty means, I submit, that it takes fourteen years or more for the pathological process to run before symptoms occur. A single transient characteristic sign of this disease lasting but a few days often occurs as long as twenty-five years before the progressive relentless disability begins, and I suggest that the process of demyelination is all over and irretrievable so soon as the progressive symptoms are present. We are faced with the inevitable scarring which long progressive and symptomless demyelination must entail. We must find some means of detecting the subjects of this disease during the symptomless stage if we are to treat them successfully. It is a remarkable fact that, while Disseminate Sclerosis affects the central nervous system indifferently and everywhere, its destructive potentiality falls upon the younger elements of the nervous system only—those that have been recently acquired, namely the pyramidal path, the co-ordinating mechanism for the upright stance and the finer movements of the hands, and for the recently acquired function of speech. The older functions of the special senses with touch, pain and temperature are never progressively destroyed.

Louping Ill in Sheep and benign Lymphocytic Meningitis in Man.

Recently accident has revealed a principle which may have an important bearing upon neurological discovery in the near future. A virus expert was working at the Lister Institute upon the disease of sheep which is called 'Louping Ill' or 'Staggers'. This is a virus disease which,

entering by the usual nasal route, passes along the nerve-threads to the cerebellum and there kills every nerve-cell, while leaving the rest of the nervous system entirely unharmed. One day this pathologist became severely ill with acute meningitis which was supposed at first to be tuberculous, from which, however, he made a complete and rapid recovery. He went to America to carry on his researches upon louping ill. In the course of a short time two of his co-workers and two of his laboratory assistants were seized with severe acute lymphocytic meningitis which rapidly recovered, and it was proved from the serological reactions and by infection of animals that the recoverable meningitis in man was due to the same virus which causes destruction of the cerebellum in sheep. I have myself recently seen three cases of acute meningitis in farmers who had been in contact with 'louping ill' infected flocks, all of whom recovered, and in the light of accidental infection among the virus workers producing recoverable meningitis, the nature of the infection seems clear. The principle is that an infection in an animal which gives rise to a definite and incurable disease in an animal, may produce in man an entirely different and curable disease. We already had this principle demonstrated in the opposite sense in the virus of herpes febrilis, which in man produces an insignificant event, but when introduced into the rabbit is apt to produce a fatal inflammation of the nervous system.

Nervous diseases are common in animals, and it is to the closer association of veterinary and human neurology and the wide investigation of the two taken together which have recently made a beginning, that we look with hope to the discovery of cause and treatment in our common nervous diseases which are at present entirely mysterious.

Bacterial Toxaemia.

The origin of disease and of tissue degeneration as the result of toxines from bacterial infection has entirely

dropped out of neurology except in the cases of the three exotoxines of tetanus, diphtheria, and botulism, which differ entirely from the elusive factor in what is commonly referred to as toxic absorption, in that they are real and can be isolated and put in a bottle and their effect proved by experiment. A few years ago the origin of pernicious anaemia and of subacute combined degeneration of the spinal cord in toxic absorption from intestinal infection seemed to have good foundation on clinical and experimental grounds, but subsequent discoveries in gastric and hepatic function have swept all such ideas away and have introduced a deprivation origin for these diseases, with highly successful means for their prevention and amelioration. Toxic absorption, at present much spoken of, will probably be similarly discarded from other realms of medicine within reasonable time. It is highly interesting that the exotoxine of tetanus does, by entering into combination with the protoplasm of the nervous system, produce a similar train of events as does the virus of hydrophobia by living within the nerve protoplasm, in one case the highest degree of over-function in the fatal spasm, in another case a complete loss of function in the toneless paralysis, just like that of severe peripheral neuritis. It seems probable that the many conditions of peripheral neuritis at present without known cause, which seem to be increasingly common among us, may be due to virus infection, and the relapsing tendency after partial recovery is like the behaviour of an encaged virus. The difficulty in this investigation is the discovery of a susceptible animal, without which we cannot find or prove a virus as the cause of disease.

Deprivation Conditions.

Deprivation conditions are likely to prove a fruitful field in the development of our knowledge of the causes of nervous disease. We already have tetany, subacute combined degeneration, beri-beri, and pellagra as due to known deprivations. The pigeon fed on polished rice

and therefore paralysed almost to death which can be restored to complete strength and action in an hour by the administration of a few drops of infusion of rice-husk, is a miracle of the effect which vitamin shortage and vitamin administration can make within the nervous system. It has recently been suggested that the commonest of nervous diseases—Disseminate Sclerosis—may prove to be a deficiency disease.

Eppinger. The 'Berry' Aneurysms.

Great advance has recently been made in our knowledge of the causes and symptoms of vasular lesions of the nervous system, following Eppinger's argument that berry-like aneurysms upon the cerebral vessels are not of spirochaetal or of other provedly infective origin. He termed these berry aneurysms congenital because they were found in children and in young animals, though it has since been shown that they may give rise to symptoms at any time of life. Turnbull has shown that they are present in at least 1 per cent. of the population. The local signs produced by such aneurysms when actively enlarging, and the signs of their slow leaking or sudden rupture, have become so well known that their presence and results in subarachnoid and subdural haemorrhage can now be diagnosed with certainty, and treatment which is often successful applied in cases which but a few years ago inevitably perished undiagnosed. The calcification of the walls in some cases makes them visible by X-ray examination with a picture which no other lesion produces, while the recently discovered method of injection into the carotid artery of a thorium compound which is opaque to X-rays has allowed of an instantograph picture of the condition of the cerebral arteries and of the presence of aneurysms which is all valuable in diagnosis. This method is also valuable in the location of tumours of the brain, because of the compression which the growth makes upon the blood-vessels.

The recent invention of Sir Henry Dale that efferent stimuli in the vegetative nervous system produce their effect by the liberation of a chemical intermediary of the choline group, and that stimulation of the sympathetic in otherwise denervated skeletal muscle results in tonic contraction, seems to me to open up the possibilities of great advance in our very scant knowledge of the pathology of the myotonias, myasthenias, and myopathies.

The Outlook in Neurology.

In the progress of neurology the all-essential labours of the Physiologist and of the Anatomist have almost reached finality. Much addition to the wealth of their discoveries is not to be expected in the future. The Bacteriologist similarly seems to have added all that is possible from his researches. Not even the absorption of hypothetical toxines troubles us as a factor in the causation of nervous disease.

The clinician and his inseparable pathologist have at the present time a fertile field in which regional diagnosis has become wellnigh perfect in which to carry on the separation begun by Thomas Parkinson a century ago, and to show the easy recognition of new and distinct nervous diseases, at present unrecognized. Thus the thirty years of the present century have given us Subacute Combined Degeneration, Dystrophia Myotonica, Amyotonia Congenita, Epiloia, Schilder's disease, Narcolepsy, the Meningeal Haemorrhages, the Cerebral Aneurysms, the many pituitary syndromes, and many other distinct and easily recognizable maladies. It is astonishing how much more common a malady becomes when it has once been well described. There is scope for a rich harvest in the future, especially in the realms of peripheral neuritis, of the muscular atrophies, and of the vascular diseases.

The Virus Worker and the Biochemist have probably the greatest immediate future before them, heralded by

their collection of the plums of the immediate past in their researches on poliomyelitis, tetany, pernicious anaemia, and insulin.

The closer association between Botanical, Veterinary, and Human Medicine, which has made a beginning, will I think have an outcome in much advance, for nervous diseases are common in animals and have not received sufficient attention.

The Psychiatrist struggles with his most difficult burden of advance almost alone. Neither Anatomist, Physiologist, Bacteriologist, Virus Worker, or Biochemist has as yet done anything material to clear the path for his progress as they have for the Neurologist. Just as the highest functions of the nervous system allow of no physiological or anatomical analysis, so do its disorders at present admit no pathological and causal conception. The primeval forest of psychiatry with no pathways cleared to look around is hard beset with an ever-growing jungle of intricate terminology.

The progress of Neurology in my lifetime has been amazing, and its present position is highly advanced for a civilization which Professor Elliot Smith insists is not yet sixty centuries removed from primitive man. And yet I doubt not that Neurology has but made a highly successful beginning.

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